EDITORIAL

Vitamin C, Thiamine and Steroids: *Ménage à Trois* or Medical *Masala*

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Introduction

We live in strange medical times. The COVID-19 pandemic has thrown up a smorgasbord of potential medical treatments, best exemplified by the case of hydroxychloroquine and azithromycin in COVID-19 patients. Limited or flawed studies, unfounded recommendations and political interests pose a dilemma for medical practitioners. *How do we use therapies that are plausible but unproven?* Before this epidemic, the therapeutic strategy that took center stage in the world of intensive care was the combination of steroids, vitamin C and thiamine. The clinical community was split, with some zealots supporting its use in all septic patients, and skeptics rolling their eyes at yet another poorly conducted study affecting bedside clinical practice.

Scientific Approach

Science can be considered as being a two-part cycle. Induction is when we explore our knowledge or data and generate new ideas and hypotheses. Deduction is when we make predictions from these new ideas and then design experiments to see if reality matches our predictions. In intensive care and medicine in general, induction is the process of hypothesis generation, and deduction involves randomized trials testing for clinical outcomes. For something to be scientifically valid, both components of the scientific cycle should be met.

A dilemma faced by many clinicians is the ambiguity between physiological plausibility and clinical outcomes. All too often, clinicians are seduced by the former and are oblivious or dismissive of the latter, especially if the latter does not match the outcome predicted by the physiology. The fundamental message in this editorial is that "*Clinical Outcomes trump Physiological Plausibility*". Once clinicians actually get this insight, it becomes easier to practice, as one simply follows the outcomes and lets the physiology catch up. It does not matter how appealing the underlying physiology of steroids, thiamine and ascorbic acid is. If it doesn't improve the clinical outcomes, it has no role in clinical medicine. End of story. Having said that, each negative trial allows us to fine-tune our physiological understanding and retry the intervention with altered regimes in more specific patient populations. The use of prone ventilation in acute respiratory distress syndrome (ARDS) and intervention in ischemic stroke are examples of earlier negative randomized controlled trials (RCTs) modifying our clinical approach till a specific strategy proved beneficial in a specific population of patients.

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What Does the Vitamin C, Thiamine and Steroid Data Show?

This particular intervention started with Marik.[1] Since then, we have had VITAMINS[2], HYVCTTSSS[3] and CITRIS-ALI.[4] The details are shown in Box 1.

There has subsequently been one negative[5] and various positive[6,7] before and after studies. These suffer from the same methodologic flaws and potential bias as the original Marik trial. We now have three "negative" RCTs, but none of them definitively closes the door on therapy. Future research may be warranted, and there are many trials awaited, such as the VICTAS trial.[8] Based on the available evidence, there is no reason to believe that a metabolic cocktail of vitamin C, thiamine and steroids improves outcomes in sepsis, but a lack of benefit cannot be completely excluded, and there is a scope for further exploration.[9]

After submission, a new RCT published on 18th August 2020 has failed to show any benefit in mortality, speed of resolution of SOFA score, acute kidney injury and ventilator-free days. There was a benefit seen in terms of shock-free days and in the cardiovascular component of the SOFA score.[10]

In this issue of IJCCM, we explore two Indian studies on the subject. The ViCTOR RCT by ZU Mohamed and colleagues specifically targeted early use of these interventions, within the first 6 hours. A confounding factor is that the use of thiamine and hydrocortisone was not restricted in the control arm. This trial with 88 patients was essentially negative, although the authors highlight a faster resolution of shock and that this finding persisted even after adjustment for steroid therapy. They noted that there was no difference in the Vasoactive Inotropic Score. The authors report but do not comment on the fact that those with the intervention spent

Box 1: The relevant clinical trials (adapted from ref. 9)

Marik[1] used a protocol of Vitamin C 1.5 g IV every 6 hours for 4 days, hydrocortisone 50 mg IV every 6 hours for 7 days, and thiamine 200 mg IV every 12 hours for 4 days.

A retrospective chart review, with a before and after design was conducted, once they realised 3 patients they thought were definitely going to expire, made a 'miraculous' recovery after receiving this cocktail therapy.

The paper presented to us with thought-provoking and, to an extent, unbelievable numbers indicating enormous difference in mortality along with some differences in secondary outcomes, such as need for renal replacement therapy and duration of vasopressors. None of the patients in the intervention group died of sepsis, but instead of complications of their underlying disease.

This was a single center, non- blinded, nonrandomized trial with a very small number of patients wherein propensity matching was used to compare the two groups. There is still a fair amount of debate about the role of steroids in septic shock. In this study, patients in the control arm also received hydrocortisone at the clinician's discretion.

Major medical decisions are usually not based on before and after studies. This study was rightly followed up with randomised controlled trials (RCTs).

VITAMINS[2]**:** This important, multicenter, open-label, parallel-group randomized trial, the first RCT of the Marik protocol, was conducted in 10 intensive care units in Australia, New Zealand, and Brazil. 216 patients out of 786 were screened for septic shock and were almost equally divided either into a treatment group which received the Marik protocol or in a control group who received hydrocortisone and at the physician's discretion were permitted to get thiamine, but were not allowed to receive vitamin C.

There was no difference in the primary outcome, time alive and free of vasopressors at 7 days (median of 122 vs 124 hours). There was no difference in all-cause mortality at 28 days (22.6% with the intervention and 20.4% with control) or at 90 days (28.6% with intervention and 24.5% with control).

Results may have been biased towards no effect, as everyone in the control group received steroids and were permitted to receive thiamine.

There was also some dispute about the initiation of therapy. The first dose of vitamin C was not given until about 12 hours, which may have been too late.

Overall, this trial diminishes the possibility that the Marik protocol is going to save any lives, but doesn't imply definitive absence of benefit.

HYVCTTSSS[3] Single-center, single-blind, randomized, controlled trial assessing 28-day all-cause mortality as they compared the Marik protocol to a control group which was given equal volume of saline, but the clinicians were not blinded.

The trial was stopped early because of "ineffectiveness" and because there was a high incidence of hypernatremia (13 patients in the treatment group and 3 in the control group).

There were no statistical differences, but the confidence intervals were huge because of the small trial size. 28-day mortality was 28% with treatment and 35% in the control group (RR 0.79, 95% CI 0.41–1.52; $p = 0.47$). The secondary outcomes were all negative.

HYVCTTSSS was too small to make any conclusive claims, it was critically underpowered as it was terminated early, but most point estimates were on the side of treatment being beneficial.

CITRIS-ALI[4]**:** A multicenter, randomized, double-blind, placebo-controlled trial that compared vitamin C (50 mg/kg every 6 hours for 96 hours) to placebo in adult ICU patients admitted with sepsis who developed ARDS.

Only 167 were enrolled out of 1262 eligible patients.

There was no difference in any of the 3 disease–oriented primary outcomes (changes in SOFA scores, CRP and thrombomodulin levels) and no difference in 43 of the 46 secondary outcomes.

One of the 3 secondary outcomes that was "statistically significant" was 28-day mortality (46% with placebo and 30% with vitamin C, $p = 0.03$, ARR 16.6% 95% CI 2–31%).

No unexpected study-related adverse events were noted.

This trial looked at a different population (ARDS) than the Marik study, making this a very select population and also used a different protocol (thiamine and hydrocortisone were excluded).

Waiting for ARDS may mean they waited too long to start therapy.

This was the first large RCT looking at vitamin C in sepsis, and it is clearly a negative study, but it doesn't eliminate the role of vitamin C in sepsis.

more time in the hospital, although they state that this difference disappeared with a *post hoc* analysis after removing outliers. It is encouraging to see this relatively well-conducted RCT emerge from Indian ICUs, and hopefully the number and quality of these studies will only increase.

The second study titled Metabolic Resuscitation by PR Reddy and colleagues looked at different components of the triple therapy and essentially found nothing of note one way or the other. This is a more problematic study to interpret, and some statistical limitations will be discussed in the methodology section. Of note, even the hydrocortisone group did not show any benefit in resolution of shock, a finding contrary to the recent larger RCTs. The total study population was 27 patients divided into 3 groups of 9 patients each. The most plausible explanation is that the study simply had too few participants in each group to make any meaningful conclusions. The authors themselves note that a sample size of nearly 200 patients was calculated, and the sample size of 27 could only be considered a hypothesis-generating study.

Methodological Considerations

A cocktail of interventions raises an interesting dilemma. Should we study a combination of interventions or should we study them separately? Combining them makes the study easier to execute and can detect beneficial synergistic effects. Unfortunately, it can result in combined therapy becoming standard practice when only one component is effective. It could miss an adverse component in one intervention, as it could be masked by a beneficial component of another intervention and vice versa. A famous advertising quote

goes as follows. "I know that 50% of what I do works. The problem is I don't know which 50%". We face the same issue in trials studying a combination of multiple therapies.

Analyzing multiple interventions also makes the statistics less reliable, especially if there is more than one comparison in the same study cohort. Let us use the example of the PR Reddy study that studied hydrocortisone (H), ascorbic acid (A) and thiamine (T). This particular study chose three arms: H, HA, and HAT. That gives them the options of comparing H vs HA, H vs HAT, and HA vs HAT. As the number of arms in a trial increases, or as the number of comparisons in a trial increases, the statistics need to be modified accordingly. Otherwise the chance of a false-positive increases. In a study using twenty comparisons, and using a cut-off of $p < 0.05$, the chance is that one comparison will be <0.05 only by random selection and not due to the intervention itself. This needs a statistical correction, either by increasing the sample size or by further decreasing the target *p* value by dividing *p* value = 0.05 by the number of planned comparisons (the Bonferroni correction). To further confound the issue, the authors could have opted to study even more groups (H, A, T, HA, HT, AT and HAT) and even more comparisons (H vs A, H vs T, H vs AT, H vs HAT, A vs T, A vs HAT, T vs HAT, HA vs HT, HA vs HAT etc. etc). To do a meaningful study evaluating three separate interventions in the same population leads to a significant chance of erroneous interpretation of the statistics.

Physiological Considerations

To understand why this particular combination may be beneficial in sepsis, one needs to delve deep into biochemistry and our evolutionary past.[11] Life needs energy, and production of energy invariably causes some collateral damage. The main mechanism to limit this collateral damage is to control energy production to match metabolic demands and to have antioxidant mechanisms to limit damage. Disappointingly, the antioxidant strategy has not proven successful as yet. It has been speculated that these interventions do not work because these reactive molecules or free radicals also serve as molecular signals. These reactive molecules are responsible for triggering the production of the cell's own antioxidants. Simply mopping up free radicals may end up doing more harm than good by preventing the production of the body's own antioxidants. An analogy of a smoke detector has been used to explain this. If one had a device that could clear the smoke in a room, the smoke detector would not be activated, and the fire alarm and fire protection mechanism would not be triggered. Therefore, the use of a smoke clearing device would adversely blunt the response in the event of a fire, and would allow damage to be greater.

Triple Therapy with Steroids, Vitamin C and Thiamine

We discuss below the relevant aspects of each component of this triple cocktail.

Steroids and Hydrocortisone

Steroids have been studied ad nauseam. Plausible mechanisms include the anti-inflammatory effects, a counter to stress-induced relative deficiency or that they sensitize catecholamine receptors. The most recent relevant trials in severe sepsis are the CORTICUS,[11] HYPRESS,[12] ADRENAL,[13] and CRICS-TRIGGERSEP.[14] The summary of their findings is that (1) low-dose steroids are ineffective in sepsis without shock, (2) low-dose steroids decrease the duration of inotropes in patients with septic shock, and (3) low-dose steroids have a mortality benefit in more severe forms of septic shock.[15] The role in community-acquired pneumonia is unclear,[16,17] but the RECENT RECOVERY TRIAL[18] showed benefit of low-dose steroids in COVID pneumonia patients requiring oxygen or mechanical ventilation. Based on the above, it seems reasonable to use low-dose steroids in septic patient with shock or in patients with hypoxemic community-acquired pneumonia. They are not indicated in sepsis without shock and in those with mild non-hypoxemic community-acquired pneumonia.

Vitamin C or Ascorbic Acid

Vitamin C is a fascinating molecule.[19] Its history and relevant information are shown in Box 2. Higher primates, guinea pigs, and fruit bats are the only living organisms that cannot manufacture their own vitamin C. We know that fruits are beneficial for health,

Box 2: Vitamin C: A brief history and fact sheet of a medical success story

Scurvy was an endemic from the time of the crusades to the first World War in sailors and soldiers deprived of fresh fruit. The mortality in these crews could vary from 50–90% depending on the duration of deprivation of fresh fruit.

The Dutch Physician Ronsseus and British Physician John Woodall recommended oranges or lemon juice to prevent scurvy as far back as 1639. The Admiralty ignored this advice. The mortality of Lord Anson's round the world trip of 1740 sailors from scurvy was 997/1995. An additional 320 died of fevers and dysentery.

In 1747, Lind performed what is now seen as the first recorded clinical RCT. Twelve sailors with scurvy, in groups of two each, got one of six options (cider, oil of vitriol, vinegar, sea water, oranges and lemons, and finally a concoction of garlic, radish Peru Balsam and myrrh). The two sailors receiving the citrus fruits made a rapid recovery, the ones receiving cider made a very mild recovery and the rest were unaffected. This was published as a Treatise on Scurvy in 1753. Sea voyagers like Captain Cook started using it in 1768–75, but it took up till 1795 for the admiralty to issue these fruits as standard. This too because of the sustained pressure of navy physicians like Gilbert Blane. As citrus fruit became a part of the standard diet, the number of hospitalization in the Hasler naval hospital drastically decreased. From over 1,000 admissions a year, it fell to only two patients between the years 1806 and 1810.

Lind himself thought the fruits prevented some form of contagion and did not actually realize that it was a nutritional deficiency.

The realization that nutritional deficiency could cause illness and that scurvy was a nutritional deficiency was explored in the 1840s by George Budd. It took till the 1920s for the "antiscorbutic factor" to be isolated from citrus fruits. It finally was named ascorbic acid in 1933.

Linus Pauling won the Nobel Prize in Chemistry in 1954 and for Peace in 1962. He was a giant of 20th century science and a politically aware human who fought for peace. In the 1970s, he severely dented his reputation by advocating Vitamin C as a cure for multiple illnesses, and also advocated doses as high as 40 g a day and for it to be used intravenously. Subsequent research showed no beneficial effect.

Early studies in the 1960s in Iowa inmates suggested that 10 mg of Vitamin C was enough to prevent clinical scurvy and intake greater than 60 mg was associated with urinary excretion of the vitamin. Later studies in the 1990s (Mark Levine) suggested that a daily intake of 200–1,000 mg was adequate and this could be met with fruit intake rather than with supplements. He also cautioned that higher doses could be dangerous.

but we are still unclear as to which micronutrients contribute to this effect. One study showed that higher levels of vitamin C in the blood levels correlated with longevity. This study has been interpreted as proving that vitamin C is directly the cause of this, while in reality, it may only be a marker of a healthier diet with adequate fruits and vegetables.

At its heart, vitamin C has one and only one action. It is an electron donor. In fact, it is an electron donor to another electron donor, iron. By regenerating Fe, it allows the reaction between Fe and O_2 to proceed. It would be no exaggeration to say that life could not have evolved if Fe did not react with O_2. Ascorbic acid, iron, and oxygen could be seen as the triumvirate of all actions of vitamin C. As this physiological reaction is so ubiquitous, vitamin C has multiple physiological roles, including protein synthesis and energy generation. It also has the potential of acting as a pro-oxidant or an antioxidant, although the physiological implication of either is unclear.

The clinical role of ascorbic acid in scurvy and in those with documented or suspected deficiency is clear, and these patients should obviously get supplements. It remains unclear whether further supplementation actually improves clinical outcomes in the general population or in the critically ill.

Thiamine or Vitamin B1

The story of thiamine, in many ways, mirrors that of vitamin C. A Japanese surgeon Kanehiro, in 1884, felt that an adequate nutritional plan would help prevent beriberi. He tested this on a navy ship by replacing a diet of white rice with other foods like milk, bread, meat, barley, and vegetable and eliminated beriberi in the process. Unlike the vitamin C story, he, from the beginning, hypothesized that beriberi was a nutritional problem and was not due to germs. Like the vitamin C story, the navy felt the new diet was not cost-effective and beriberi returned to claim sailors' lives. Just like vitamin C was initially called the "antiscorbutic factor", thiamine was called the "antineuritic factor". Thiamine was the first vitamin to be described, leading to the name Vitamin B1. Thiamine acts as a cofactor for many enzymes, principally pyruvate dehydrogenase. Like ascorbic acid and other vitamins, it has multiple roles, and deficiency leads to specific disease. Thiamine deficiency can cause wet beriberi due to high-output cardiac failure, dry beriberi due to peripheral neuropathy, and central nervous system illness, including Wernicke's encephalopathy, Korsakoff psychosis, and optic neuropathy. Thiamine deficiency should be suspected in malnourished patients and in those with alcoholism.

The clinical role of supplementation of thiamine is obvious in those with beriberi or Wernicke's encephalopathy and in those with documented or suspected deficiency. It remains unclear if further supplementation actually improves clinical outcomes in the general population or in the critically ill.

Summary

There are many physiological reasons to believe that certain molecules could modify or enhance our host response in sepsis. Hydrocortisone, Vitamins C, and B1 could all plausibly do this. There is also reason to believe that combination therapies will be more beneficial than single ones, although this approach also has potential problems, both in terms of physiology and in terms of statistical analysis. Despite some promise in initial small studies, the current large RCTs have failed to show a meaningful clinical benefit, and the newer studies in this issue of IJCCM are in keeping with these observations. If one is a liberal user of medicines, then one could justify its routine use by noting that it is not disproven, it is safe, and cheap. If one is a restrictive practitioner of intensive care, one could safely avoid using this combination until new studies show a specific regime working in a specific population. The authors currently use steroids as per the protocols and regimes of the positive trials, i.e., 200 mg hydrocortisone daily in septic hypotensive patients and 6 mg dexamethasone in those with hypoxemic community-acquired pneumonias. Appropriate vitamin replacement is used in those with potential or suspected deficiency, but we do not routinely use high-dose vitamin replacements as a form of metabolic resuscitation.

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